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Stimulating Parameters and De-synchronization in Vagus Nerve Stimulation Therapy for Epilepsy

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Abstract. The influence of the stimulation parameters on the de-synchronization of small world Hindmarsh-Rose (H-R) neural network is numerically investigated in the vagus nerve stimulation therapy for epilepsy. The simulation shows that synchronization evolves into de-synchronization when a part of neurons (about 10 percent) is stimulated with a pulse current signal. The network de-synchronization appears to be sensitive to the stimulation parameters. For the case of the same stimulation intensity, those weakly coupled networks reach de-synchronization more easily than strongly coupled networks. There exist an optimal stimulation interval and period of continuous stimulation time when other stimulation parameters remain invariable.

1. Introduction
As an approved adjunctive therapy of refractory epilepsy, vagus nerve stimulation (VNS) [1] has shown beneficial clinical effects in treating epilepsy [2,3] and has recently shown promise in treating patients with major depression [4-6]. VNS is applied through an electrode wrapped around the left vagus nerve in the neck. The electrode is connected to a subcutaneous pulse generator that can deliver intermittent electrical current for variable on and off times at different intensities, frequencies, or pulse-widths. Thus, VNS can be administered with an array of at least five different use parameters (intensity, frequency, pulse-width, on-time, and off-time) [7]. Scientists have not fully understood the neurobiological effects of these use parameters, either alone or in combination, although VNS at different intensities has different effects on emotional memory [8] and pain perception [9,10].

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Following the discovery by Zabara in 1985 that VNS could stop seizures, a lot of research work has been done so as to better understand the use parameters. Researchers used animal studies with electroencephalogram (EEG) and electromyography (EMG) to determine the use parameters, which were most likely to be effective for epilepsy [11]. As a result, they were employed in initial clinical trials in epilepsy [2,3], and adopted for the current clinical studies in patients with depression [4-6]. Still, there is incomplete understanding of the regional neurobiological effects of different VNS use parameters.

Since VNS is a relatively invasive procedure; it is difficult to acquire data from healthy control subjects. It should be also noted that VNS studies performed acutely (within 24 h after VNS is initiated) or chronically (after months or years of ongoing VNS) have shown different results, suggesting that there are dynamic brain changes associated with VNS [4]. More information is needed about the effects of different VNS parameters on regional brain activity to help set optimal parameters in clinical use. Knowing whether VNS at different parameters evokes similar spatial patterns of brain activation would greatly advance knowledge of the basic mechanisms of action of VNS [4], accelerate the exploration of the effects of different stimulation parameters and regimen, and, possibly, extend its application to other disorders.

In addition, synchronization is a natural property of interacting oscillators or functional units, intensively studied in many physical [12], engineering [13], chemical [14] and biological [15-18]. However, synchronization is not always desirable. In fact, several neurological diseases, such as epilepsy, essential tremor and tremor in Parkinson’s disease, are caused by synchronized populations of oscillatory neurons [18]. Thus, there is a significant clinical need for mild stimulation techniques, which restore desynchronized dynamics in networks of oscillatory neurons [19,20].

Despite that VNS is an important option in pharmaco-resistant epilepsy; its mechanism of action remains unclear. The observation that VNS desynchronized the EEG activity in animals suggested that this mechanism could be involved in VNS antiepileptic effects in humans. Indeed VNS decreases spiking bursts, whereas its effects on the EEG background remain uncertain [5]. Thus it is of interest and of importance to study how different stimulation parameters affect the destruction of the complete synchronization in VNS [7]. In the present paper, we shall investigate numerically the effect of the stimulation frequency, stimulation intensity, period of continuous stimulation time and stimulation interval on the de-synchronization.

2. Model
Among the many proposed biophysical models, the HR models has still been considered as a valid framework for exploring neural excitability for biophysical models, due to its relative simplicity combined with the fact that it embodies the major features of membrane potential evolution. Here we study the emergence of temporal interdependencies in a small world network of coupled HR neurons. To simplify the computation, we restrict our analyses to “rings” of neurons, which is used to in a small world network. It has been established that periodically driven nonlinear oscillators or a system of coupled nonidentical oscillators can achieve phase, or have stronger coupling and time-lag synchronization [21–24]. Another reason to adopt small world network is that the organization of the synaptic connections within cortical regions is neither a lattice of nearest-neighbor connections nor completely randomly connected [25]. Basing on the ideas proposed by Watts and Strogatz, a small world networks is constructed in the following way: we adopt HR neuron models to structure a network of synaptically connected, starting with a ring of N vertices, each connected to its 2K nearest neighbors by indirect edges, and then each local link is visited once with the rewiring probability p it is removed and reconnected to a randomly chosen node. Duplicate and self-connected edges are forbidden. After the whole sweep of the entire network, a small world graph is constructed with a linked degree $k = 2K / N$. To represent epilepsy with the network synchronization status and represent anti-epilepsy effect with de-synchronization, we investigate numerically the effect of the stimulation frequency, stimulation intensity, period of continuous stimulation time and stimulation interval on the de-synchronization in vagus nerve stimulation therapy for refractory epilepsy. For the
small world neural networks of the HR neurons, the dynamics of the system can be described by \[19,21,22\]

\[
\begin{align*}
\dot{x}_i &= y_i - ax_i^3 + bx_i^2 - z_i + I_{0i} + \frac{\varepsilon}{K} \sum_{j=1}^{N} (x_j - x_i) \\
\dot{y}_i &= c - dx_i^2 - y_i \\
\dot{z}_i &= r(s(x_i - \chi) - z_i)
\end{align*}
\]

(1)

where \(x\) represents membrane action potential, \(y\) is a recovery variable associated with the fast current, \(Na^+\) or \(K^+\), and \(z\) is a slow adaptation current such as \(Ca^{2+}\). \(a, b, c, d, r, s\) and \(\chi\) are constants; in the following numerical simulations, let \(a = 1.0, b = 3.0, c = 1.0, d = 5.0\), \(r = 0.006, s = 4.0, \chi = -1.6\). All neurons are connected via bi-directional coupling having strength \(\varepsilon\). \(N\) is the number of neurons (set as 1000 throughout this investigation). \(K\) is the number of actual connections per neuron (the number of synapses per neuron, set as 50). Equation (1) is solved with the fourth-order accurate Runge-Kutta method; statistics were carried out by using \(1.0 \times 10^5\) times of calculation with the time step of \(1.0 \times 10^{-3}\). The initial transients of the model were discarded (first 500 steps). The parameter \(I_{0i}\) represents an external current including static direct current and a pulse stimulus current delivered externally to the \(i\)th neuron.

\[
I_{0i} = 1.4 + g_p \delta(t - t_k)
\]

(2)

here, the static direct current is set as about 1.4, and \(g_p\) is the pulse stimulation intensity. \(t_k\) is the time of \(k\)th pulse and the recursive equation is described as

\[
t_{k+1} = t_k + T
\]

(3)

where \(T\) is the inter-spike intervals of input pulses and \(f = 1/T\).

The mean network synchronization error \(<e>\), can be calculated by averaging \(e\) over time, at time \(t\), \(e\) read as follow

\[
e = \frac{\sum_{i=1}^{N} e_i}{N} \quad i = 1, 2, \cdots, N
\]

(4)

the network status is in the synchronization when \(<e> \to 0\), or the network status is in the desynchronization. The synchronization error of \(i\)th neuron \(e_i\) is calculated based on the following formula

\[
e_i = \sqrt{(x_i - \bar{x})^2 + (y_i - \bar{y})^2 + (z_i - \bar{z})^2}
\]

(5)

where \(\bar{x} = \frac{\sum_{i=1}^{N} x_i}{N}, \bar{y} = \frac{\sum_{i=1}^{N} y_i}{N}\) and \(\bar{z} = \frac{\sum_{i=1}^{N} z_i}{N}\), and the index \(i\) varies from 1 to \(N\)

3. Numerical Simulation and Results

Firstly, we consider a situation without pulse stimulation. Figure 1 presents the relationship between the mean network synchronization error and the coupling intensity for this self-coupling neural network. It is seen that under the condition without pulse stimulation the synchronization occurs when the coupling intensity exceeds 6. In other words, the networks activity is driven into synchronization rapidly when the coupling intensity \(\varepsilon \geq 6\).
Figure 1. The mean network synchronization error $<e>$ as a function of the coupling intensity $\varepsilon$ without pulse stimulation.

Figure 2. The evolution of network synchronization error with time.

In the presence of pulse stimulation, the network synchronization may evolve into desynchronization. For example, after a portion (about 10 percent) of neurons is stimulated by a pulse current signal, the network evolves from synchronization to de-synchronization. Figure 3 plots the network synchronization error as a function of time while the stimulation intensity $g_\rho$ is 0.01 and the stimulation frequency $f$ is 30 Hz. There is no pulse current signal when time $t$ is between 0 and 1620 with $\varepsilon = 10$. However, this simulation is devoted to mimicking a real clinic experiment in which the period of continuous stimulation time is 30 seconds and the stimulation interval is 5 minutes. Figure 2 also shows that the state of network activity transits from synchronization to de-synchronization after $t = 1620$, and about 10 percent of neurons are stimulated by a pulse current signal.
An important topic is how different frequencies and intensities affect the destruction of the complete synchronization in VNS therapy for patients with epilepsy. Using numerical simulations, we have found that the network de-synchronization is sensitive to the stimulation frequency and intensity. This observation is consistent with the clinical experimental results [7]. Figure 3 reveals the relationship of mean network synchronization error and the stimulation frequency at different stimulation intensities. It can be seen from Fig. 3 that the higher the stimulation frequency, the larger the mean network synchronization error, which results in an increase of the destruction of the network synchronization by the pulse signal. In other words, the de-synchronization degree increases with increase in the stimulation frequency. Comparing the results at three different stimulation intensities, one can also find that the larger the stimulation intensity, the larger the destruction degree of the pulse to network synchronization.

It is also of interest to investigate how different stimulation frequencies and stimulation intensities affect the various individuals in VNS therapy for patients with epilepsy. To simulate this phenomenon numerically, we shall use different coupling intensities to represent various individual features. Moreover, to clarify the effect of coupling intensity on the mean network synchronization error, we shall set the stimulation intensity as constant in the situation. Figure 4 shows the relationship of mean network synchronization error and the stimulation frequency at different coupling intensities (which are taken as 8, 10 and 12, respectively). It can be found that there is an increase of de-synchronization with increase in the stimulation frequency, regardless of the coupling intensity.

![Figure 3](image_url)  
Figure 3. The mean network synchronization error versus the stimulation frequency with $\varepsilon = 10$ at various stimulation intensities $g$: 0.01 (square), 0.05 (circle) and 0.08 (triangle).
Figure 4. The mean network synchronization error as a function of the stimulation frequency with \( g_p = 0.01 \) and different \( \varepsilon \): 8 (square), 10 (circle) and 12 (triangle).

Figure 5. The mean network synchronization error as a function of the stimulation intensity, under the same stimulation frequency (30 Hz) and different coupling intensities: 8 (square), 10 (circle) and 12 (triangle).

We also investigate the influence of the stimulation intensity on the mean network synchronization error. Fig. 5 presents the relationship of mean network synchronization error and the stimulation intensity at the same stimulation frequency and different coupling intensities (equal to 8, 10 and 12, respectively). It is obvious that the de-synchronization of the network becomes more and more distinct when the stimulation intensity increases, regardless of how the coupling intensity value is used. Meanwhile, at the same stimulation intensity, the de-synchronization of the network is more...
prominent with smaller coupling intensity than that with larger coupling intensity. In other words, the de-synchronization of the network at weaker coupling intensity is more sensitive to increasing the stimulation intensity.

Figure 6. The mean network synchronization error as a function of the stimulation intensity, under the same stimulation frequency (30 Hz), coupling intensity (10), stimulation interval (240) and different period of continuous stimulation time: 10 (square), 20 (circle), 30 (triangle) and 40 (asterisk).

Finally, we investigate the influence of the period of continuous stimulation time $\tau$ and stimulation interval $\Delta t$ on the mean network synchronization error. Fig. 6 shows the relationship of mean network synchronization error and the stimulation intensity at the same stimulation frequency $f = 30\,\text{Hz}$, coupling intensity $\varepsilon = 10$, stimulation interval $\Delta t = 240$ and different period of continuous stimulation time $\tau$ (equal to 10, 20, 30 and 40, respectively). The longer period of continuous stimulation time $\tau$ becomes, the better effect of de-synchronization is. This phenomenon is much more distinct when the stimulation intensity goes larger.

Fig. 7 presents the relationship of network synchronization error and the stimulation intensity at the same stimulation frequency $f = 30\,\text{Hz}$, coupling intensity $\varepsilon = 10$, period of continuous stimulation time $\tau = 30$ and different stimulation interval $\Delta t$ (equal to 180, 240, 300 and 360, respectively). Obviously, with the increasing of stimulation intensity, the mean network synchronization error goes largeness. In other words, the effect of de-synchronization becomes distinct. At the same time, it seems that there exists an optimal stimulation interval at round $\Delta t = 240$ with period of continuous stimulation time $\tau = 30$. In a word, the mean network synchronization error goes to maximum when the stimulation interval $\Delta t$ is about 240, namely, we obtain the optimal effect in vagus nerve stimulation therapy for epilepsy.
Figure 7. The mean network synchronization error as a function of the stimulation intensity, under the condition: stimulation frequency (30 Hz), period of continuous stimulation time (30), coupling intensity (10) and at the different stimulation interval: 180 (square), 240 (circle), 300 (triangle) and 360 (asterisk).

Fig.8. The relationship of mean network synchronization error versus the stimulation interval, under the same stimulation frequency $f = 30\,Hz$, stimulation intensity $g_p = 0.01$, coupling intensity $\epsilon = 10$ and period of continuous stimulation time $\tau = 30$. 
Fig. 9. The mean network synchronization error as a function of the period of continuous stimulation time, under the conditions: stimulation frequency (30 Hz), stimulation intensity (0.01), coupling intensity (10) and stimulation interval (240).

In order to explore the question of the optimal stimulation interval, we fix all other parameters (let stimulation frequency $f = 30$ Hz, coupling intensity $\varepsilon = 10$, stimulation intensity $g_p = 0.01$, period of continuous stimulation time $\tau = 30$) and obtain the relationship of mean network synchronization error versus stimulation interval (show in Fig.8). From Fig.8, it is clear that there exists an optimal stimulation interval at round $\Delta t = 240, 330, 450, 510, and 570$ with period of continuous stimulation time $\tau = 30$.

Fig.9 presents the relationship of mean network synchronization error and the period of continuous stimulation time at the same stimulation frequency $f = 30$ Hz, stimulation intensity $g_p = 0.01$, coupling intensity $\varepsilon = 10$, stimulation interval $\Delta t = 180$. One can see that the changes of the mean network synchronization error are sensitive to the period of continuous stimulation time. The optimal periods of continuous stimulation time are $\tau = 40$ and 70.

4. Conclusion
In general, adopting the small world H-R neural network, we have numerically studied the influence of the stimulation intensity and frequency on the destruction of the complete synchronization in the vagus nerve stimulation therapy for patients with epilepsy. By means of simulations, we have found that the synchronization of network can evolve into de-synchronization when a part (about 10 percent) of neurons are stimulated with pulse current signal. The simulations have shown that the network de-synchronization is sensitive to the stimulation frequency and intensity. The higher the stimulation frequency is, the larger the degree of de-synchronization. The de-synchronization of larger stimulation intensity to network is more distinct than that of weaker stimulation intensity. At the same stimulation intensity, the de-synchronization of network is more prominent with small coupling intensity than that with larger coupling intensity. The networks of larger coupling intensity are less sensitive to the stimulation intensity than that of smaller coupling intensity. We find that there exist the optimal stimulation interval and optimal period of continuous stimulation time when the other stimulation parameters remain certain.
The influence of pulse-width, however, on the destruction of the complete synchronization is beyond the scope of this paper and will be investigated in next work.

REFERENCES